J Antimicrob Chemother 2014; **69**: 1633–1641
doi:10.1093/jac/dku031 Advance Access publication 18 February 2014

Journal of Antimicrobial Chemotherapy

Understanding variability with voriconazole using a population pharmacokinetic approach: implications for optimal dosing

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Received 19 September 2013; returned 18 November 2013; revised 23 December 2013; accepted 27 January 2014

Objectives: Voriconazole exhibits highly variable, non-linear pharmacokinetics and is associated with a narrow therapeutic range. This study aimed to investigate the population pharmacokinetics of voriconazole in adults, including the effect of *CYP2C19* genotype and drug–drug interactions.

Methods: Non-linear mixed effects modelling (NONMEM) was undertaken of six voriconazole studies in healthy volunteers and patients. Dosing simulations to examine influential covariate effects and voriconazole target attainment (2–5 mg/L) stratified by CYP2C19 phenotype were performed.

Results: We analysed 3352 voriconazole concentration measurements from 240 participants. A two-compartment pharmacokinetic model with first-order oral absorption with lag time and Michaelis–Menten elimination best described voriconazole pharmacokinetics. Participants with one or more *CYP2C19* loss-of-function (LoF) alleles had a 41.2% lower V_{max} for voriconazole. Co-administration of phenytoin or rifampicin, St John's wort or glucocorticoids significantly increased voriconazole elimination. Among patients receiving 200 mg of voriconazole twice daily, predicted trough concentrations on day 7 were <2 mg/L for oral and intravenous regimens for 72% and 63% of patients without *CYP2C19* LoF alleles, respectively, with 49% and 35% below this threshold with 300 mg twice daily dosing. Conversely, these regimens resulted in 29%, 39%, 57% and 77% of patients with *CYP2C19* LoF alleles with voriconazole trough concentrations ≥5 mg/L.

Conclusions: Current dosing regimens for voriconazole result in subtherapeutic exposure in many patients without *CYP2C19* LoF alleles, suggesting the need for higher doses, whereas these regimens result in supratherapeutic exposure in a high proportion of patients with reduced CYP2C19 activity. These findings support the essential role of therapeutic drug monitoring in ensuring efficacious and safe voriconazole exposure.

Keywords: antifungals, azoles, CYP2C19

Introduction

The triazole antifungal voriconazole exhibits broad-spectrum antifungal activity and is indicated in the treatment of a range of pathogenic and opportunistic mycoses.[1] Highly variable, non-linear pharmacokinetics complicate the clinical use of voriconazole, with hepatic metabolism occurring primarily via the polymorphic drug-metabolizing enzyme CYP2C19 and, to a lesser extent, CYP3A4 and CYP2C9.[2] Drug interactions, patient age and *CYP2C19* genotype have been found to contribute to the pharmacokinetic variability observed with voriconazole.[2,3]

Since FDA and European Medicines Agency (EMA) approval in 2002, a growing number of studies have investigated exposure–response relationships with voriconazole. These studies have identified a relationship between low voriconazole exposure and higher rates of treatment failure, in addition to higher rates of neurotoxicity at higher exposure, establishing a narrow therapeutic range for voriconazole.[4–10] Notably, a recent randomized, controlled trial demonstrated improved treatment outcomes in patients who received therapeutic drug monitoring of voriconazole,[11] affirming the importance of optimizing voriconazole exposure in patients.

Population pharmacokinetic analyses are a valuable technique for characterizing the pharmacokinetics of medicines, identifying and quantifying sources of patient-related (demographic and genotypic) and clinical (drug interactions and disease-related) pharmacokinetic variability, and providing dose recommendations for clinical practice based on model simulations. Using a range of pharmacokinetic studies undertaken in healthy volunteers and patients, this study aimed to characterize the

pharmacokinetics of voriconazole in adults and evaluate the influence of demographic, genotypic and clinical covariates on voriconazole exposure using a population pharmacokinetic approach. Furthermore, this study aimed to investigate the ability of current dosing recommendations for voriconazole to achieve efficacious and safe systemic exposure within the therapeutic range using simulations from the final pharmacokinetic model.

Methods

Pharmacokinetic data and participants

Pharmacokinetic data and relevant clinical data from six voriconazole studies in healthy volunteers or patients receiving voriconazole for the treatment or prophylaxis of fungal infections were available for analysis. Information on study design, population, pharmacokinetic data and participant demographics is included in Table 1. Further details on these studies have been described previously.[3,4,12–15]

Population pharmacokinetic modelling

The pharmacokinetic data were analysed using non-linear mixed effects modelling with NONMEM 7.2 (Globomax LLC, Hanover, MD, USA). Differential equation solvers were used throughout model development (ADVAN6 or ADVAN13 subroutines), with final model development using ADVAN6. The gfortran compiler (version 4.6) was used with NONMEM, with Pirana (version 2.7-2.8; http://www.pirana-software.com/) and Perl-Speaks-NONMEM (version 3.5.3; http://psn.sourceforge.net/) used for model execution. Data visualization was performed with R (version 2.15.2; http://www.r-project.org/), Xpose (version 4.4; http://xpose.sourceforge.net/) and Microsoft Excel 2010. The first-order conditional estimation method with interaction was used throughout model development.

Structural model and interindividual variability (IIV)

Pharmacokinetic models incorporating either one or two compartments with first-order oral absorption and linear, non-linear (Michaelis–Menten) or parallel linear and non-linear elimination were investigated. An improvement in model fit with the addition of an oral absorption lag time was evaluated. Models were initially developed with richly sampled intravenous and oral voriconazole pharmacokinetic data (studies 1–3, 5 and 6; Table 1); sparsely sampled concentration–time data were then incorporated into the model (study 4, Table 1) with appropriate goodness-of-fit testing.

IIV in voriconazole pharmacokinetic parameters was evaluated using exponential error models. A logit model was used for bioavailability to ensure physiologically plausible individual estimates not exceeding

Table 1. Voriconazole pharmacokinetic data and participant demographics

	Study 1[3]	Study 2[12]	Study 3[13]	Study 4[4]	Study 5[14]	Study 6[15]
Study type	bioavailability and effect of *CYP2C19* genotype	interaction with short-term ritonavir	interaction with St John's wort	TDM of voriconazole	time-course of CYP3A inhibition	steady-state pharmacokinetics and metabolism
Study population	healthy volunteers	healthy volunteers	healthy volunteers	patients treated with voriconazole	healthy volunteers	patients treated with voriconazole
Sample size	20	20	15	146	8	31
Voriconazole dosing	single 400 mg orally and 400 mg intravenously	single 400 mg orally	single 400 mg orally	multiple dose intravenously/orally (50 mg twice daily–600 mg twice daily)	multiple dose orally (400 mg twice daily on day 1 and 200 mg twice daily on days 2–9)	first (400 mg) and/or multiple dose (200 mg twice daily) orally
Samples per dose interval	oral, 29; intravenous, 32	15	11	1[a]	14	6–10
Age[b] (years)	25 (20–38)	26 (19–37)	26 (22–35)	56 (18–88)	29 (22–36)	56 (19–72)
Weight[b] (kg)	71 (58–103)	76 (47–85)	80 (68–93)	68 (39–113)	77 (60–86)	66 (50–115)
Sex (%)						
female	8 (40)	7 (35)	0	59 (40)	2 (25)	12 (39)
male	12 (60)	13 (65)	15 (100)	87 (60)	6 (75)	19 (61)
CYP2C19 (%)						
EM/HUM[c]	8 (40)	8 (40)	9 (60)	NR	7 (87.5)	24 (77)
PM/HEM[d]	12 (60)	12 (60)	6 (40)	NR	1 (12.5)	7 (23)

TDM, therapeutic drug monitoring; NR, not recorded.
[a]One to 28 samples per patient.
[b]Median (range).
[c]Participants with *CYP2C19*1/*1* (EM) or **1/*17* genotype (HUM).
[d]Participants with *CYP2C19*1/*2* (HEM), **2/*17* (unknown phenotype) or **2/*2* genotype (PM).

100%. Proportional, additive and combined additive and proportional residual error models were evaluated.

Covariate model

Participant-specific covariates such as body weight, age and sex, as well as potential drug–drug interactions, including co-administered proton pump inhibitors (pantoprazole, omeprazole, esomeprazole, rabeprazole), phenytoin, rifampicin, short-term ritonavir (300 mg twice daily for 2 days), St John's wort and glucocorticoids, were investigated. Only biologically plausible parameter–covariate relationships were explored. Continuous covariates were examined in the first instance using linear parameter–covariate relations, with the exception of body weight on V_{max}, which was also tested using allometric scaling with an exponent of 0.75. Categorical covariates were parameterized as a multiplicative effect on the associated structural parameter. A full model, including all potential parameter–covariate relationships, was developed from the final covariate-free model; covariates were then tested by individual deletion from the full model. Parameter–covariate relationships that resulted in a significant increase in objective function value (OFV) ($\geq$10.83) upon deletion from the full model were retained in the final model.

Model selection and validation

Model development and selection were guided by goodness-of-fit criteria, including significant decreases in OFV between nested models, goodness-of-fit plots, precision of parameter estimates and visual predictive checks (VPCs). A decrease of 3.84 in OFV ($P<0.05$) for one degree of freedom was considered statistically significant.[16]

Prediction- and variability-corrected VPCs (pvcVPCs) were used for model validation.[17] Similar to VPCs, pvcVPCs allow a graphical assessment of the predictive performance of a model by comparing model simulations with observed data in terms of central trend and variability, but differ in that both model simulations and observed data are normalized to correct for differences arising from independent variables (e.g. differences in dose, time or covariates) as well as the typical population variability in each bin.[17] One thousand simulated datasets of individuals from the original dataset were compared with prediction- and variability-corrected observed concentrations. Bootstrapping procedures were not feasible due to very long model runtimes.

CYP2C19 genotype

Information on *CYP2C19* genotype was available for participants from five of the six studies included in the analysis (Table 1). Participants were assigned a CYP2C19 phenotype based on the presence of loss-of-function (LoF) (*CYP2C19*2*) or gain-of-function (GoF) alleles (*CYP2C19*17*): heterozygous ultra-rapid metabolizer (HUM; *CYP2C19*1/*17*), extensive metabolizer (EM; *CYP2C19*1/*1*), heterozygous extensive metabolizer (HEM; *CYP2C19*1/*2*), poor metabolizer (PM; *CYP2C19*2/*2*) or unknown phenotype (*CYP2C19*2/*17*) (adapted from Scott *et al.*[18]). Among the five studies where *CYP2C19* genotype was known, no participants were identified with other *CYP2C19* LoF alleles (**3* allele) or with two GoF alleles (*CYP2C19*17/*17*).

Dosing simulations and effect of covariates

Using the $SIM command with NONMEM, dosing simulations with parameter estimates from the final voriconazole pharmacokinetic model were performed to assess the probability of voriconazole trough concentration target attainment, defined as a trough concentration between 2 and 5 mg/L.[4] Simulations were stratified by CYP2C19 phenotype. Dosing simulations were designed to examine trough concentrations following an oral or intravenous loading dose on day 1 of treatment (400 mg twice daily) as well as on day 7 of treatment following 200 mg twice daily, 300 mg twice daily or 400 mg twice daily oral or intravenous voriconazole dosing (each with a loading dose for the first two doses). A range of voriconazole concentration cut-off values (1, 1.5, 2 and 5 mg/L) were investigated to examine the probability of sub- or supratherapeutic concentrations with each dose regimen. One thousand patient simulations were performed for each dose regimen.

The influence of significant covariates in the final model on voriconazole trough concentrations was also investigated. One thousand patient simulations stratified by CYP2C19 phenotype were performed to assess the impact of each covariate on voriconazole trough concentrations on day 7 of treatment, following standard oral voriconazole dosing (400 mg twice daily for two doses followed by 200 mg twice daily). Simulated trough concentrations with and without each covariate were compared with the therapeutic range for voriconazole.

Results

Model development and validation

Three thousand three hundred and fifty-two voriconazole concentration measurements from a total of 240 participants were included in this analysis. A two-compartment pharmacokinetic model with first-order oral absorption with an absorption lag time and Michaelis–Menten elimination adequately described the dataset; models incorporating linear elimination resulted in significant increases in OFV whereas models incorporating parallel linear and non-linear elimination did not improve goodness of fit over non-linear elimination alone. A combined proportional and additive residual error model was used. Goodness-of-fit plots and pvcVPCs used throughout model development indicated acceptable model fit (data not shown). The pvcVPCs of the final model (Figure 1) indicated good predictive performance, with acceptable agreement between prediction- and variability-corrected observed data and model-simulated CIs for the median and 5th and 95th percentiles.

Parameter estimates and associated standard errors for the structural model, IIV and residual variability from the final model are shown in Table 2. High IIV in voriconazole pharmacokinetics was observed, particularly in the Michaelis–Menten constant (K_m) (CV% 64.5) and volume of distribution in the central compartment (83.4%). Voriconazole bioavailability was estimated to be 94% with IIV of 36.7%.

Voriconazole V_{max} was found to be significantly higher in healthy volunteers compared with patients receiving voriconazole. The extent of this effect was characterized using a categorical covariate (Table 3). A difference in voriconazole elimination between single-dose and multiple-dose data was also investigated; however, this resulted in numerical difficulties with the model, possibly due to co-linearity with the covariate differentiating healthy volunteers and patients.

Effect of CYP2C19 genotype

The effect of *CYP2C19* genotype on voriconazole elimination was estimated using a binary categorical CYP2C19 phenotype, with participants allocated to a phenotype group based on the presence of one or more *CYP2C19* LoF alleles. The difference in V_{max} in participants with an HEM or PM phenotype for CYP2C19 was estimated as a multiplicative difference compared with V_{max} in participants with an EM or HUM phenotype. To prevent potential

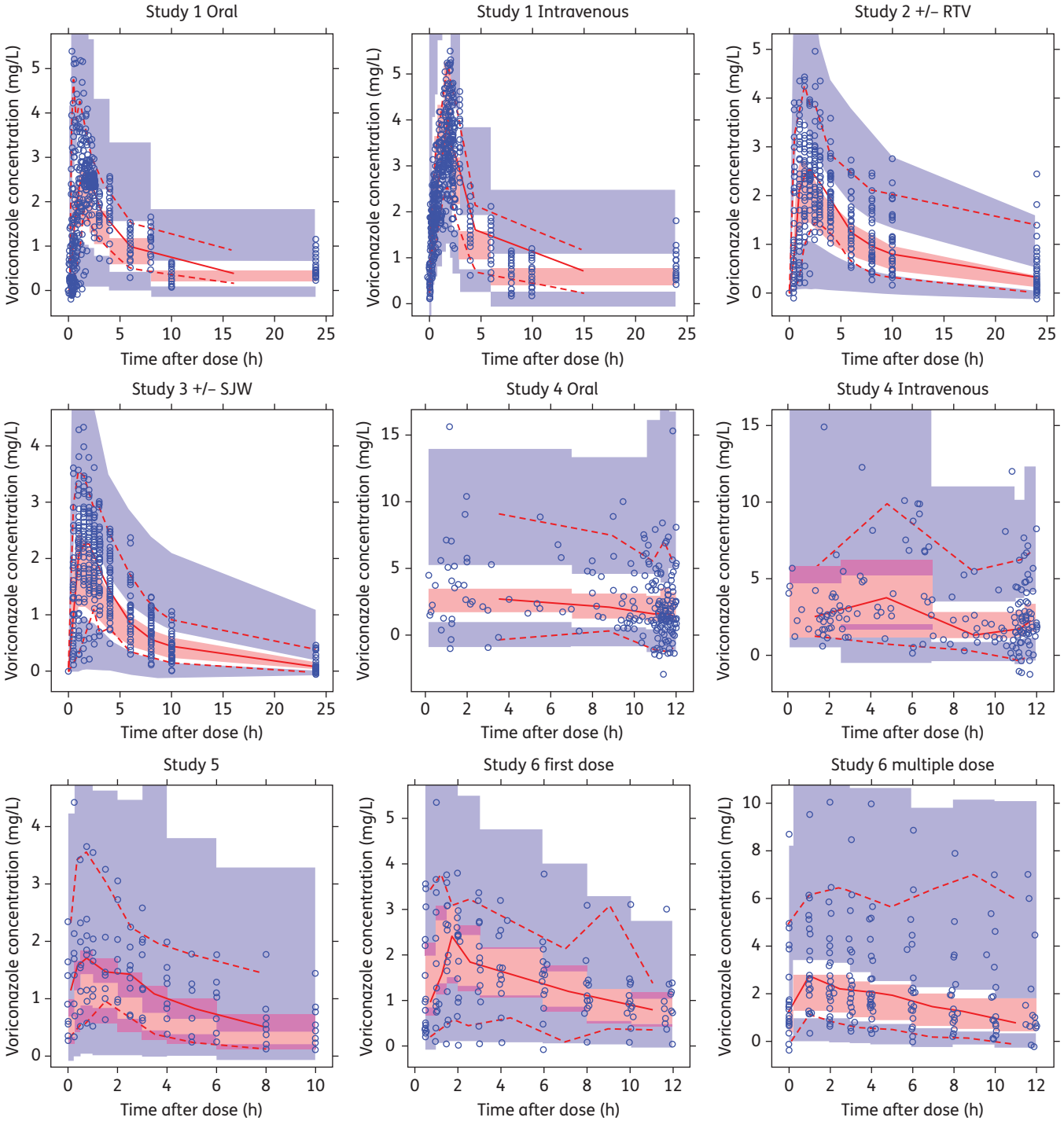

Figure 1. pvcVPCs of the final model stratified by study and route of administration. Prediction- and variability-corrected observed concentrations are shown as open circles, with the continuous and lower and upper broken lines showing the median and 5th and 95th percentiles of the observed data, respectively. The shaded areas represent 95% CIs for the model-predicted median and 5th and 95th percentiles constructed from 1000 simulated datasets of individuals from the original dataset. RTV, ritonavir; SJW, St John's wort. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

bias in the estimated effect of CYP2C19 function on voriconazole, an additional parameter was estimated in participants where *CYP2C19* genotype was not known (study 4).[19]

Participants with one or more *CYP2C19* LoF alleles had, on average, a 41.2% lower V_{max} for voriconazole compared with participants with no LoF alleles (Table 3).

Table 2. Parameter estimates of the final population pharmacokinetic model

Parameter	Population estimate	Precision (RSE%)
Structural model		
V_{max} (patients) (mg/h)	43.9	20.8
K_m (mg/L)	3.33	33
V_c (L)	27.1	12.7
V_p (L)	127	6.4
k_a (h^{-1})	0.53	8.4
absorption lag time (h)	0.162	0.8
F (%)	94.2	2.9
Q (L/h)	35.1	7.4
IIV (CV%)		
V_{max}	26.8	12.7
K_m	64.5	10.4
V_c	83.4	14.3
V_p	38.1	15.6
k_a	41.6	18.3
F	36.7	14.8
Q	37.4	14.4
Residual variability		
proportional error (CV%)	33.8	4.6
additive error (mg/L)	0.005	6.3

V_c, volume of distribution in the central compartment; V_p, volume of distribution in the peripheral compartment; k_a, first-order absorption rate constant; F, bioavailability; Q, intercompartmental clearance; RSE%, relative standard error expressed as a percentage.

Table 3. Significant covariate effects on the maximum rate of voriconazole metabolism (V_{max}) included in the final model

Parameter	Effect on V_{max} (% increase/ decrease)	Precision (RSE%)	ΔOFV upon deletion
≥1 *CYP2C19* LoF allele	−41.2	17.1	37.5
Short-term ritonavir	−42.9	8.6	436
St John's wort	107	12.1	373
Phenytoin/rifampicin	203	15.3	80.9
Prednisone/prednisolone	36.6	33.6	30.4
Methylprednisolone	56.4	26.2	60.9
Dexamethasone	55.7	77.7	25.4
Healthy volunteer (versus patient)	111	24.7	15.6

RSE%, relative standard error expressed as a percentage; ΔOFV, change in the NONMEM-derived OFV.

Dosing simulations and target attainment stratified by CYP2C19 phenotype

The probability of voriconazole target trough concentration attainment stratified by dosing regimen and CYP2C19 phenotype is shown in Table 4. Among patients with a CYP2C19 EM/HUM phenotype, oral voriconazole loading doses on day 1 resulted in trough concentrations ≥2 mg/L in 33% of patients. Standard oral dosing of 200 mg of voriconazole twice daily resulted in a small decline in this proportion by day 7 of therapy (28%). Higher-dose oral regimens (voriconazole at 300 mg twice daily or 400 mg twice daily) were associated with a higher probability of target attainment (51% and 70%, respectively); however, the probability of supratherapeutic concentrations ≥5 mg/L also increased (21% and 41%). Lower voriconazole trough concentration targets (1 or 1.5 mg/L) resulted in higher probabilities of target attainment, as did the use of intravenous rather than oral voriconazole dosing regimens.

Voriconazole target attainment was substantially higher among patients with a PM/HEM phenotype for CYP2C19, as was the risk of trough concentrations ≥5 mg/L associated with the possibility of voriconazole adverse effects. Oral voriconazole loading doses on day 1 were associated with a 59% probability of trough concentrations ≥2 mg/L on day 1, with this figure increasing to 63% on day 7 following 200 mg twice daily dosing; however, 29% of patients would be expected to achieve concentrations ≥5 mg/L. Higher voriconazole dose regimens were associated with a very high probability of trough concentrations ≥5 mg/L among patients with a PM/HEM phenotype for CYP2C19, with a 57% and 77% probability for 300 mg twice daily oral and intravenous regimens, and 76% and 93% for 400 mg twice daily oral and intravenous regimens.

The predicted median voriconazole concentration–time profile over the first 7 days of treatment from 1000 simulated patients following standard oral dosing, stratified by CYP2C19 phenotype, is shown in Figure 2. Clear evidence of the saturation of voriconazole metabolism was predicted among a significant proportion of patients with a CYP2C19 PM/HEM phenotype.

Effects of covariates on voriconazole pharmacokinetics

Significant covariates included in the final pharmacokinetic model for voriconazole are shown in Table 3. Co-administration of phenytoin or rifampicin, St John's wort, methylprednisolone, dexamethasone and prednisone or prednisolone was associated with significant increases in the estimated voriconazole V_{max}, whereas short-term ritonavir reduced V_{max}. Most covariate effects were estimated with good precision; lower precision was observed for co-administration of dexamethasone (relative standard error 77.7%). The effect of these medicines on predicted voriconazole trough concentrations in relation to the therapeutic range, stratified by CYP2C19 phenotype, is shown in Figure 3. Co-administration of phenytoin, rifampicin and St John's wort was associated with large reductions in voriconazole exposure, with most patients achieving trough concentrations far below the therapeutic range, particularly among those with an EM/HUM phenotype for CYP2C19. A more moderate reduction in voriconazole exposure was observed with glucocorticoid co-administration. Short-term ritonavir co-administration was associated with large increases in voriconazole trough concentrations, increasing the probability of concentrations exceeding the therapeutic range, particularly among patients with a PM/HEM phenotype for CYP2C19.

Tested parameter–covariate relationships that did not result in a significant increase in OFV (≥10.83) when removed from the full

Table 4. Probability of voriconazole target attainment from model simulations of patients receiving voriconazole (1000 patients per dose regimen)

	Percentage probability by voriconazole dosing regimen and CYP2C19 phenotype							
	400 mg twice daily day 1		200 mg twice daily day 7		300 mg twice daily day 7		400 mg twice daily day 7	
Trough concentration (mg/L)	oral	intravenous	oral	intravenous	oral	intravenous	oral	intravenous
CYP2C19 EM/HUM								
≥1	67	83	51	60	72	83	81	93
≥1.5	50	63	37	47	60	73	75	89
≥2	33	47	28	37	51	65	70	85
≥5	3	4	5	8	21	29	41	57
CYP2C19 PM/HEM								
≥1	86	98	79	92	89	99	93	100
≥1.5	72	89	71	85	84	97	91	99
≥2	59	75	63	78	81	96	88	99
≥5	8	13	29	39	57	77	76	93

Day 7 dosing regimens included a loading dose of 400 mg of voriconazole twice daily for two doses on day 1. Intravenous regimens were simulated as a 1, 1.5 and 2 h intravenous infusion for the voriconazole 200 mg, 300 mg and 400 mg regimens, respectively.

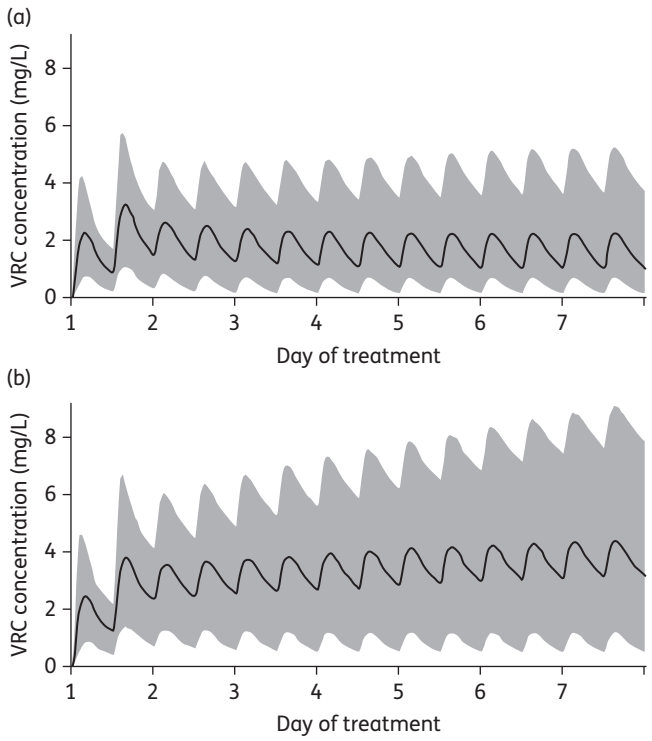

Figure 2. Predicted median concentration–time profile over the first 7 days of treatment derived from 1000 simulated patients with a CYP2C19 EM/HUM phenotype (a) or PM/HEM phenotype (b). Standard oral dosing (400 mg twice daily for two doses followed by 200 mg twice daily) was used in both groups. The black continuous line represents the median, with the grey shaded area extending to the 10th and 90th percentiles. VRC, voriconazole.

model included body weight with V_{max}, body weight with central volume of distribution, proton pump inhibitor co-administration with V_{max}, sex with V_{max}, sex with central volume of distribution and age with V_{max}.

Discussion

This study provides a comprehensive analysis of the population pharmacokinetics of voriconazole and the influence of a number of significant drug–drug interactions, with dosing simulations providing the first report of voriconazole target attainment stratified by CYP2C19 phenotype.

CYP2C19 genotype is a key intrinsic determinant of voriconazole exposure.[3,20,21] This study demonstrates that among patients without *CYP2C19* LoF alleles, a majority are predicted to require higher dosing, of at least 300 mg twice daily, to achieve recommended trough voriconazole concentrations (≥2 mg/L). Conversely, patients with *CYP2C19* LoF alleles have substantially increased voriconazole exposure, with a significant proportion (29%–39%) at risk of potentially toxic voriconazole concentrations of ≥5 mg/L with 200 mg twice daily dosing. It is important to note that no individuals with known homozygous GoF alleles (*CYP2C19*17/*17*) were included in this analysis. Voriconazole exposure in individuals with this genotype is yet to be investigated, but would be expected to be further reduced compared with heterozygous ultra-rapid metabolizers and extensive metabolizers.[22,23]

Despite this, genotype information is not typically available in clinical practice and, if investigated, may not become available until after the patient has begun treatment. While routine genotyping of *CYP2C19* may be of use for voriconazole, particularly in determining initial dosing, overlap between and high variability in exposure within phenotype groups is observed with voriconazole,

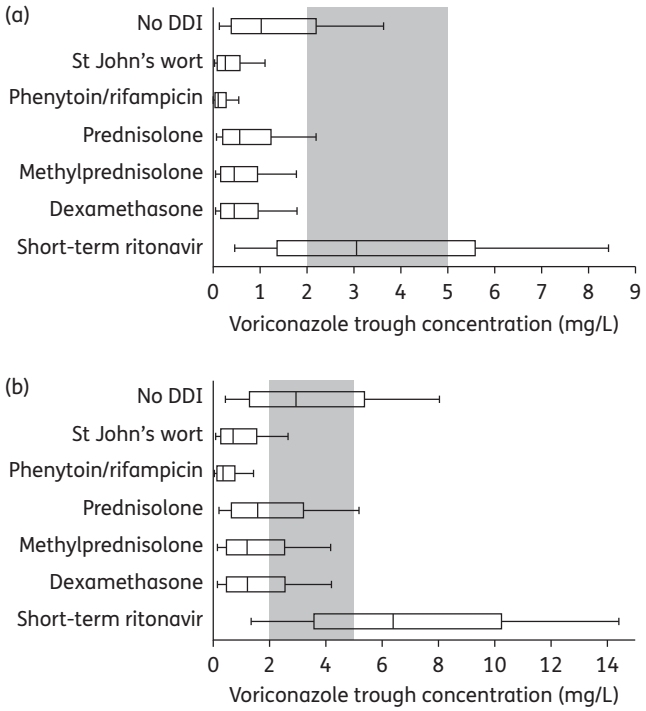

Figure 3. Effect of co-administered medicines on predicted voriconazole trough concentration on day 7 of therapy from 1000 simulated patients with a CYP2C19 EM/HUM phenotype (a) or PM/HEM phenotype (b) presented as an adjusted box plot. Standard oral dosing (400 mg twice daily for two doses followed by 200 mg twice daily) was used in both groups. The central box line represents the median trough concentration and the lower and upper box ends represent the 25th and 75th percentiles, respectively, with the bars extending to the 10th and 90th percentiles. The grey shaded area shows the therapeutic range (2–5 mg/L). DDI, drug–drug interaction.

limiting the utility of *CYP2C19* genotype in predicting dose requirements in an individual patient. In the context of the narrow therapeutic range associated with voriconazole, these findings support the crucial role of therapeutic drug monitoring of voriconazole in ensuring efficacious and safe systemic exposure.

Several population pharmacokinetic analyses have recently been published for voriconazole in adults, each using different methods to characterize voriconazole elimination.[9,24,25] As in the present study, Hope[25] described voriconazole elimination using a Michaelis–Menten model using data from healthy volunteers and patients, whereas Pascual *et al.*[9] used linear elimination in their analysis of voriconazole patient data. The model developed by Friberg *et al.*[24] included data from immunocompromised children and adolescents as well as healthy adults, and used a parallel linear and non-linear elimination model. Figure 4 provides a comparison of the predicted clearance with increasing voriconazole concentration from the present study and with these previously published models.[9,24–26]

As demonstrated in Figure 4, the parameter estimates reported by Friberg *et al.*[24] predict significantly higher voriconazole clearance than was observed in patients in this study, irrespective of CYP2C19 phenotype. This finding may be attributable to the healthy volunteer rather than patient adult study population used by Friberg *et al.*;[24] significantly faster elimination among healthy volunteers compared with patients was also identified in the present analysis. Furthermore, a similar finding is apparent in the FDA *Clinical Pharmacology and Biopharmaceutics Review* of voriconazole in data submitted by the original manufacturer in 2002. Among pooled Phase I data from 402 healthy volunteers, the median of average steady-state voriconazole concentrations (presumably untimed) was 0.95 mg/L; the median concentration among 1053 patients from Phase II/III studies was 2.49 mg/L,[27] suggesting slower voriconazole elimination among patients.

No relationship between body weight and voriconazole pharmacokinetics was identified in this analysis. This finding has been reported in other analyses,[9,25] including the original population pharmacokinetic analysis submitted to the FDA by the manufacturer,[27] and does not support the use of weight-based dosing regimens with voriconazole in adults. This result is reinforced by increasing evidence of high voriconazole exposure in obese patients dosed according to actual body weight,[28] and similar exposure in obese and non-obese individuals when weight-independent voriconazole dosing is used.[29] In adult patients weighing <40 kg, the manufacturer recommends the oral maintenance dose should be halved,[30] mirroring the dosing regimen used in Phase II/III studies.[27] In this analysis, only one individual weighed <40 kg, precluding an analysis of voriconazole exposure in patients weighing <40 kg. Therefore, this study supports the use of weight-independent dosing regimens of voriconazole in adult patients weighing ≥40 kg.

Voriconazole oral bioavailability was estimated to be 94% in this analysis, although significant IIV was observed. Voriconazole bioavailability in healthy volunteers has been estimated between 83% and 96%,[3,21,30] with other population analyses reporting values of 86%, 64% and 63%.[9,24,25] Despite high bioavailability, the risk of subtherapeutic voriconazole exposure is higher with oral dosing regimens (Table 4), suggesting that increased monitoring of voriconazole concentration during intravenous to oral switch is prudent.

A number of drug–drug interactions significantly influenced voriconazole elimination in this analysis. Phenytoin, rifampicin and St John's wort were associated with a substantial reduction in voriconazole exposure, with glucocorticoid co-administration associated with a smaller reduction in exposure. We previously identified an association between glucocorticoid co-administration and lower voriconazole concentrations, with *in vitro* and some *in vivo* evidence supporting an inductive effect of glucocorticoids on CYP2C19 and/or CYP3A.[4,31–33] A limitation of the effect of phenytoin, rifampicin and glucocorticoids on voriconazole elimination is that these medicines were co-administered primarily among patients with sparse pharmacokinetic sampling (study 4), which may have affected the precision of these estimates, although some patients with more detailed sampling (study 6) were also co-administered glucocorticoids. Furthermore, the magnitude of interaction observed with rifampicin or phenytoin on voriconazole exposure is similar to that observed in crossover interaction studies.[30]

Short-term ritonavir co-administration (300 mg twice daily for 2 days) was associated with significantly increased voriconazole exposure, as previously described in a study included in this analysis.[12] The effect of ritonavir on voriconazole pharmacokinetics is complex, and is both time and dose dependent.[12,34] In a study of

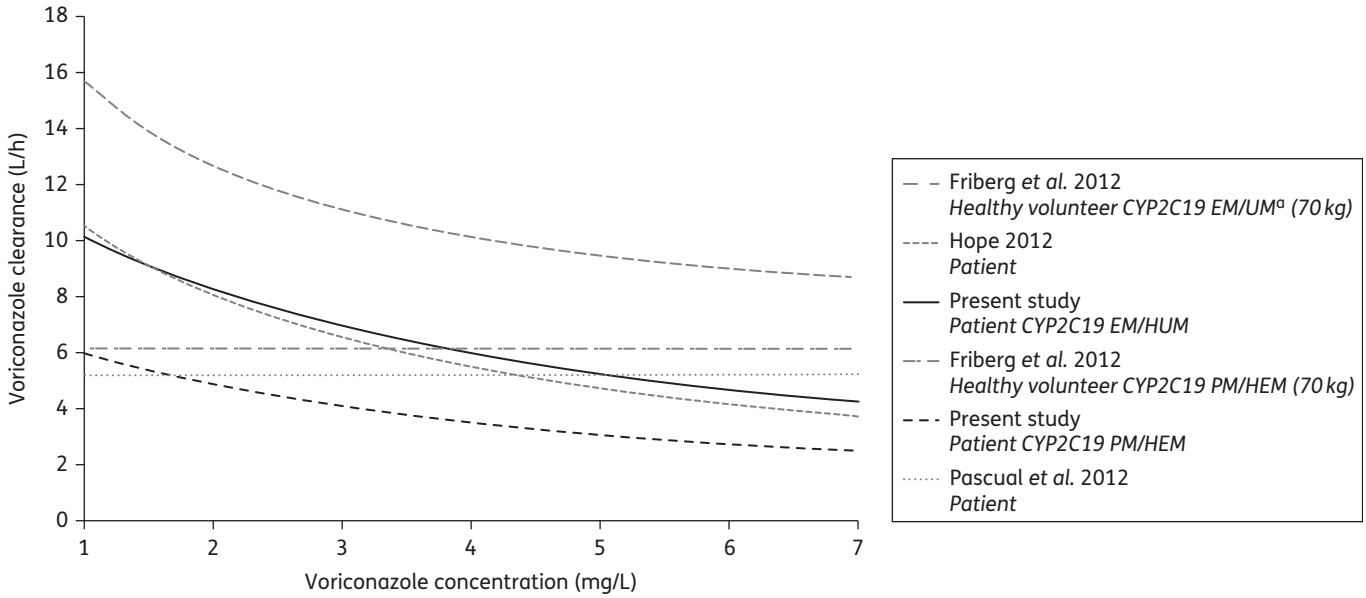

Figure 4. Predicted voriconazole clearance with increasing concentration in the present study and from the studies of Friberg *et al.*,[24] Hope[25] and Pascual *et al.*[9] For models incorporating non-linear or parallel linear and non-linear elimination, clearance was estimated from V_{max} and K_m as $CL = V_{max}/(K_m + C)$, where C = voriconazole concentration.[26] [a]Friberg *et al.*[24] classified individuals with the *CYP2C19*17* allele as ultra-rapid metabolizers (UM phenotype); it is not specified whether a distinction between individuals heterozygous and homozygous for the *17 allele was made (HUM versus UM phenotype), as was the case in the present study.

longer-term ritonavir co-administration (400 mg twice daily for 20 days with voriconazole co-administered for 10 days), Liu *et al.*[34] observed an 82% reduction in mean voriconazole AUC, with a 39% reduction seen with low-dose ritonavir (100 mg twice daily). The increased voriconazole exposure observed with short-term ritonavir co-administration is likely due to inhibition of CYP3A by ritonavir, whereas the significantly decreased exposure seen with longer-term co-administration is attributable to potent induction of CYP2C19.[35] Taken together, these results indicate ritonavir may initially increase the risk of concentration-dependent adverse events with voriconazole; however, longer-term co-administration is likely to compromise voriconazole efficacy due to low systemic exposure.

The highly variable, non-linear pharmacokinetics and the prevalence of significant drug–drug interactions with voriconazole render empirical dose adjustment inaccurate and non-intuitive. Combined with the narrow therapeutic index, these factors support the potential benefit of a Bayesian feedback strategy to individualize dose, a concept that has been demonstrated in liver transplant recipients receiving oral voriconazole[36] and in a separate analysis with intravenous voriconazole.[37]

However, a number of challenges remain in the application of computer-based forecasting strategies to the use of voriconazole. The most significant of these is likely to be the inherent difficulty of accurately estimating non-linear elimination (V_{max} and K_m) in an individual patient in the clinical setting. Routine trough concentration monitoring will not necessarily identify a patient with saturated voriconazole elimination until more than one concentration measurement is available, revealing an ongoing and potentially rapid increase in trough concentrations. Furthermore, with standard voriconazole dosing many patients may display relatively linear pharmacokinetics due to concentrations remaining predominantly below K_m, which would not provide sufficient individual information on V_{max} and K_m unless higher doses (with accompanying concentration sampling) were used to unmask saturable elimination. Future work will examine the feasibility and predictive performance of this model when used as part of a Bayesian feedback strategy for voriconazole.

Voriconazole is an important antifungal agent with challenging pharmacokinetics, a narrow therapeutic index and significant drug–drug interactions. In addition to characterizing the pharmacokinetics of voriconazole and the impact of a range of demographic and clinical covariates, this study demonstrates the wide variability in dose required to achieve efficacious and safe voriconazole exposure. In light of this, therapeutic drug monitoring is a crucial tool in managing the numerous challenges associated with voriconazole therapy.

Funding

This study was supported by internal funding from the Faculty of Pharmacy at the University of Sydney. M. J. D. is supported by an Australian Postgraduate Award.

Transparency declarations

G. M. and J. W.: The Department of Clinical Pharmacology and Pharmacoepidemiology Heidelberg has received a grant from Pfizer (New York, USA) to establish and make available an HPLC method for the determination of voriconazole in plasma that is validated according to FDA standards. J. E. R. has received a grant from Pfizer to develop and validate a voriconazole assay. M. J. D. and A. J. M.: none to declare.

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